REMARKS

The Office Action of June 27, 2002 was received and carefully reviewed. As a result, reconsideration and withdrawal of the currently pending rejections is requested for the reasons advanced in detail below.

Claims 1-11 were pending prior to the above amendment. By the above amendments, claims 1-11 have been replaced with claims 12-21.

With regard to the Examiner's rejection of claims 1-5, under 35 U.S.C. 101, as reciting a non-statutory class of invention, i.e., "use of" claims, the Applicants have adopted the Examiner's suggestion and provided two separate sets of claims to replace claims 1-5. The first set is new claims 12-14 (similar to original claims 1, 2 and 5) which are drawn to a composition comprising the naphthoquinone derivative of Formula 1. The second set is new claims 15-17 (again similar to original claims 1, 2 and 5) which are drawn to a method of use of the naphthoquinone derivative of Formula 1 to manufacture a medicament for use in treating and/or controlling tuberculosis in a patient caused by *Mycobacterium tuberculosis*. Since the instant application was filed under 35 U.S.C. 371 as a national stage of International Application PCT/IB00/00837, the Applicants assert that new claims 12-17 have unity of invention, under PCT Articles 3(4)(iii) and 17(3)(a), PCT Rule 13.1, and 37 C.F.R. 1.475, with new claims 18-21 (which are similar to the original method of treating claims 6-11) in that each set of claims shares the same "special technical feature," i.e., the naphthoquinone derivative of Formula 1. Examination of claims 12-17, along with claims 18-21, is respectfully requested.

With regard to Examiner's rejection of claims 6-11, under 35 U.S.C. 103(a) as being obvious over the Khan et al article entitled "Antibiotic Action of Constituents of Root Bark of *Euclea Natalensis A.DC.*," the Applicants respectfully traversed this rejection for at least the reasons elaborated upon below.

Initially, it is noted that the Applicants have cancelled original claims 1-11 while setting forth new claims 12-21 which narrow the scope of the claimed invention to the

naphthoquinone derivatives of Formula I in which R represents an OH group and R1 represents a methyl group (that is, old claims 1, 3 and 4 and claims 6, 8 and 9 were combined).

Regarding the Examiner's rejection, the Examiner stated that the Khan et al reference teaches the naphthoquinones, such as 7-methyljuglone, diospyrin and plumbagin, (applicants' preferred naphthoquinones), which are asserted to possess antibacterial and antifungal activity. However, plumbagin is a well known naphthoquinone that is not covered by the presently amended claims as neither R2 nor R3 in the compound of the claims is a methyl group, as is the case with plumbagin. Accordingly, the Applicants' comments are directed to addressing the Examiner's objection to preferred naphthoquinones, i.e., 7-methyljuglone and diospyrin.

The Khan et al reference includes in Table 1, on page 198, a list of bacteria against which 7-methyljuglone and diospyrin were tested together with the results of the tests. This table indicates that 7-methyljuglone was found not to be active against *Pseudomonas aeruginosa* or *Escherichia coli*, but was active against *Clostridium welchii*, *Staphylococcus aureus* and *Neisseria gonorrhoea*. By contrast, diospyrin was found not to be active against any of these bacteria. The authors go on to state:

> "The active principles isolated were 7-methyljuglone (I), diospyrin (II) ...These showed...a varied degree of antibiotic activity against a number of selected microorganisms as shown in Table 1...Although it is not known at this stage, without clinical evaluations, whether the rootbark is active or not possible effectiveness against sores, purulent lesions and skin infections could be attributed to the activity of mamegekinone against *Staphylococccus aureus*. 7-methyljuglone demonstrated activity against *Neisseria gonorrhroea* (24 mm zone inhibition)... 7-methyljuglone with its significant *in vitro* antigonococcal activity could **possibly** give curative properties to the rootbark against gonorrheoea..." (emphasis added)

Thus, the very document cited by the Examiner shows numerous occasions where 7-methyljuglone and diospyrin would appear to give little likelihood of success as anti-bacterial agents since each demonstrated very different activities against very different bacteria. The Applicants believe that the teachings of the Khan et al reference amount to

nothing more than an "obvious to try" approach to the compounds of Khan et al with no reasonable likelihood of success as an antibacterial agent against *Mycobacterium tuberculosis* being expected by one of ordinary skill in the prior art at the time of the invention. (See MPEP Chapter 2143.02) The Khan et al article even refuses to assert the compounds (within the scope of the claimed invention) are anti-bacterials for *in vivo* use against the limited set of bacteria showing *in vitro* effectiveness "without clinical evaluation." Such teachings by Khan et al are clear indications that it would not have been obvious to one of ordinary skill in the prior art that the compounds of the claimed invention can be formulated into therapeutically effective compositions against a very different bacteria, i.e., *Mycobacterium tuberculosis*, tested by Khan et al.

In addition to the above, the Applicants have established that a small change in the structure of a naphthoquinone molecule may cause a substantial difference in its activity against different microorganisms. In their previous experiments, a compound isolated from *Euclea natalensis*, octahydroeuclein (see Fig 1. below), which is a closely related molecule to diospyrin, has been found not to be active against *Mycobacterium tuberculosis*.

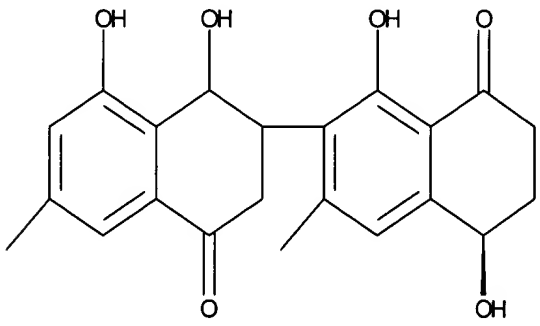


Fig. 1. Octahydroeuclein

Likewise, a structural analogue of diospyrin, i.e., dimeric form of lawsone, (see Fig 2.) was synthesized in the laboratory and then tested against *M. tuberculosis* and also

found to be inactive. This observation is consistent with the enormous influence of structural modification on the biological activity of the bisnaphthoquinoid molecule. The test data for the above related molecules can be submitted if the Examiner so desires.

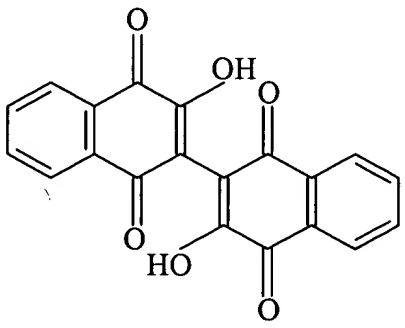


Fig. 2. Dimeric lawsone

As is evident from the above discussion, not only does the Khan et al reference show occasions where 7-methyljuglone and diospyrin (which the Applicants have discovered are both active against *Mycobacterium tuberculosis*) have very different activities against very different bacteria, but the Applicants' own previous experiments have provided naphthoquinone derivatives with structures very similar to diospyrin but which do not show activity against *Mycobacterium tuberculosis*. Accordingly, the Applicants believe that the activity of the naphthoquinone derivatives of the presently claimed invention against *Mycobacterium tuberculosis* are unexpected by one of ordinary skill in the prior art, and, therefore, this activity would not have been obvious at the time of the invention from the teachings of the Khan et al reference, or any other of the prior art of record for that matter.

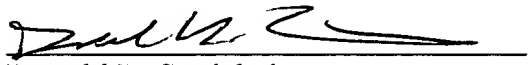
Thus, the applicants maintain their view that compositions containing therapeutically effective amounts of the naphthoquinone derivatives of Formula I, in which R is OH and R1 is methyl, would be effective in the treatment/control of *Mycobacterium tuberculosis* is new and inventive.

Consequently, the rejection of claims 6-11, under 35 U.S.C. 103(a), as being

obvious over the combination of teachings of the Khan et al article is improper and must be withdrawn.

In view of the foregoing, the present application should now be in condition for allowance and a notice to that effect is respectfully requested. However, if the Examiner finds any issue to remain unresolved after considering this response, or should any new issue arise, she/he is invited to call the undersigned to expedite the prosecution by working out any such issue by telephone.

Respectfully submitted,



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